

Please delete paragraph 17.

Attachment A is a replacement specification containing pages 1 through 22.

Attachment B is a clean copy of the amended paragraphs 6, 10-12, 14-16, 26-28, 31-39, 41-52 and new claims 26-57.

Attachment C is a marked-up copy of the amended specification clearly indicating the changes made.

The "Remarks" section comprises comments regarding the detailed Office Action.

Remarks

A replacement copy of the Specification wherein the paragraphs are now numbered is attached to the present response to facilitate the recovery of the amendments on a paragraph replacement basis. This document is identical to the document originally filed on November 16, 2001.

The changes in the disclosure and claims were made as to eliminate clerical errors, to avoid ambiguities and thus provide clearer language, to rectify technical errors, and to claim the invention in a more clear, complete, and appropriate manner.

No new matter has been added.

Respectfully,



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ATTACHMENT A
Replacement Specification

Please replace pages 1 through 19 as originally filed with new pages 1 through 22.

ATTACHMENT B

Clean Replacement Paragraphs

Please replace the previously provided paragraphs from the replacement specification with the following clean paragraphs:

0006, 0010, 0011, 0012, 0014, 0015, 0016, 0026, 0027, 0028, 0031, 0032, 0033, 0034, 0035, 0036, 0037, 0038, 0039, 0041, 0042, 0043, 0044, 0045, 0046, 0047, 0048, 0049, 0050, 0051 and 0052.

Please delete paragraph 0017.

Please delete ~~Claims~~ 1-25.

Please add Claims 26-57.

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[0006] Laser radiation, on the other hand, possesses several attributes that make it particularly well suited for the task of analyzing heterogeneous materials. In so-called laser ablation, a focused laser pulse provides locally a very large power density that transforms a small amount of solid material directly into a vapor plume suitable for further analysis. The possibility of concentrating laser radiation on a very small surface enables the sampling and analysis of heterogeneous materials with very good lateral resolution (down to a few micrometers). The separate analysis of successive laser ablation events at a same position on the solid material also enables a depth-resolved analysis, the depth reached by each laser pulse ranging from tens of nanometers to tens of micrometers depending on the laser characteristics and material type.

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[0010] In order to establish a detailed depth profile, one needs to perform several compositional measurements at different depths in the material. To avoid repeatedly carrying the sample to a separate instrument for the determination of depth, and the subsequent need for precise repositioning of the sample in the laser ablation apparatus, one can resort to a preestablished calibration of the crater depth on the basis of the cumulative number of laser pulses. In this way, the compositional analysis for a given laser pulse is

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made to correspond to a given depth. In cases where the sample comprises a coating and a substrate, both having significantly different ablation rates (ablated depth per laser pulse), different calibrations can be used for the coating and substrate, and an interpolation can be used for the interface region. This procedure assumes that the ablation rate is the same for the study sample and the calibration sample, which in particular requires sufficient stability of the laser pulse energy and beam radial profile. However, this approach is limited to relatively simple cases. It would not be applicable to samples for which the ablation rate varies in a continuous manner as a function of depth, or to complex multilayer samples.

[0011] An example of such a problematic case is the compositional mapping of pharmaceutical tablets by LIPS. The core of pharmaceutical tablets consists of a compacted blend of different components (active agent, lubricant, inactive excipient, etc.) originally in powder form, and may be coated with a film (typically containing titanium dioxide and other ingredients). US Patent 5,781,289 July 14, 1998 by Sabsabi and Bussi re describes the use of LIPS for the analysis of preselected components in homogeneous pharmaceutical compositions, for example for the quantification of the average active agent concentration in tablets. Although such a spatially-averaged analysis by LIPS can find several uses in pharmaceutical process development and control, a mapping capability would prove useful for another set of problems: (i) assessment of powder blend uniformity by the mapping in tablets of the drug, lubricant or other components, or (ii) evaluation of coating homogeneity and thickness across the surface of the tablet. In the latter case, a depth-profiling capability is required. However, because of the particular laser-matter interaction that occurs in tablets and of the granular nature of tablets, the corresponding ablation rate is usually very large compared to that in a metal for instance. Whereas on a metal tens of nanometers are ablated per laser pulse, 10-15 μm can be ablated per pulse in a tablet coating and up to 50-100 μm per pulse in the core of tablets. As a result, the aspect ratio (depth-to-diameter ratio) of the laser-produced crater can grow very large, thus significantly modifying the ablation rate at each successive pulse (because of a decreasing laser energy density on the crater surface due to an increasing exposed surface, or because of increasing confinement of the ablated matter and of plasma in the crater). A depth calibration in this case would not be possible. The same would be true if instead of using LIPS, the analysis proceeded through the transfer of the ablated matter to an auxiliary discharge and detection system (as in LA-ICP-OES or LA-

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ICP-MS). The same would also be true of any other analysis based on direct solid sampling by laser ablation where the ablation rate varies continuously as a function of depth, or where the multilayer structure of the sample is so complex as to preclude any calibration.

[0012] Combining laser ablative sampling and optical sensing of the sampling position in a single integrated apparatus would provide a means of determining in real time the depth of laser-produced craters for each laser pulse if desired, thus eliminating the need for depth calibration. US Patent 6,259,530 B1 July 10, 2001 by Monsallut describes a method and device, based on optical heterodyne interferometry, for measuring the depth of craters obtained by the bombardment, with a beam of primary ions, of a sample placed in the analysis chamber of a physico-chemical analyzer, such as a SIMS instrument. This invention relates to depth-profile analysis by ion-based techniques in high-vacuum chambers. It does not feature an integrated optical system performing both functions of laser-ablative sampling and crater-depth evaluation. Moreover, this method requires the optical paths to follow an incident direction inclined in relation to the surface of the sample (thus freeing the space needed for the circulation of secondary ions extracted from the sample). Consequently, this configuration would not be adequate for the characterization of craters with large aspect ratio, since shading might occur.

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[0014] Therefore, there is a need to provide an optical tool for the non-contact, in-situ and real-time measurement of the depth of laser-produced craters, for each laser pulse or at any pulse number interval desired. The in situ and real time measurement of depth eliminates the need to periodically characterize the crater depth in another separately-located instrument, or to rely on a calibration of depth (based on cumulative pulse number) for a given material, or finally to resort to an interpolation of such calibrations for describing the interface between two materials.

[0015] In accordance with the invention there is provided a method of compositional analysis of a heterogeneous material of one or more components, comprising the steps of: directing a pulse of laser radiation at a target of the heterogeneous material to ablate an amount thereof, and to form an ablation crater having a depth; determining the concentration of one or more selected components in the heterogeneous material ablated

AB from the target; (c) measuring in situ the depth of the ablation crater other than in dependence upon time gated imaging data of the directed pulse of laser radiation, and (d) determining a composition of the heterogeneous material at the depth.

AK [0016] In accordance with another aspect of the invention there is provided an apparatus for compositional analysis of a heterogeneous material of one or more components, comprising: a laser source for producing an ablation beam of laser pulses of sufficient fluence to ablate an amount of the heterogeneous material from a target under study and thereby to form an ablation crater of a depth; a spectrometric device for detecting and determining the concentration of one or more selected components in the heterogeneous material ablated from the target; and an optical device for measuring in situ the depth of the ablation crater using other than time gated imaging.

[0026] Figure 5 shows the evolution of spectral line intensities obtained by LIPS as a function of the number of laser pulses.

AS [0027] Figure 6 shows the evolution of the crater profile obtained with 220 successive line scans of the depth measurement beam. The 200 ablation laser pulses occurred from the 10th to the 210th line scan.

[0028] Figure 7 shows the evolution of crater depth as a function of the scan number. The 200 ablation laser pulses occurred from the 10th to the 210th line scan of the depth measurement beam.

AK [0031] In addition to these two functions, a complete analytical apparatus must also include the means for analysing the composition of the ablated matter. In the LIPS technique, the luminous plasma formed above the specimen surface concomitantly with the ablation event is analysed through optical emission spectrometry. Different elements present in the sample are identified by the emission of characteristic spectral lines at well-known wavelengths. Furthermore, their concentration is deduceable from the spectral line intensity, following calibration using certified standard materials. In general, time gating of the detection device is used so as to eliminate the very intense and less useful continuous and ionic emission of the first instants of the laser-produced plasma. In other techniques, the

sample is enclosed in an ablation chamber comprising a window through which the ablating laser is focused. After extinction of the laser-produced plasma, the ablated and atomized matter recondenses in aerosol form and is transported in a gas stream, for example argon, toward an auxiliary continuous plasma device, for example an inductively-coupled plasma (ICP). The ablated material is optionally introduced directly into the auxiliary plasma device, for example a microwave-induced plasma device, which connects directly with the laser ablation chamber, as described by Uebbing et al. in *Spectrochim. Acta Part B*, vol. 47, 1992, p. 611. The aerosol is again atomized and ionized in the auxiliary plasma device, with some of the atoms and ions being brought to excited states. The detection of excited atoms or ions by optical emission spectroscopy as in LIPS, for example, is then be used to identify and quantify the elements present. Alternatively, the quantitative elemental analysis is performed following the extraction and mass-separation of ions by electrostatic methods, for example using a mass spectrometer. Although in the present embodiment the ablated matter is introduced in such a way into an auxiliary plasma to perform the spectrochemical analysis, the preferred embodiments described below rather integrate the LIPS scheme. It allows more flexibility in terms of sample shape, size and even movement since the sample does not have to be enclosed in an ablation chamber.

[0032] The depth at which each measurement is made is preferably evaluated in-situ and in real time. Depth evaluation is optionally based on confocal microscopy, laser triangulation or interferometry using a short coherence length light source - also referred to as white light interferometry or optical coherence tomography. In confocal microscopy, light is sent through a pinhole and the light collected through the same pinhole after reflection by the object is monitored. The surface location is determined by noting that the collected light is at maximum intensity when the image of the pinhole is in focus on the surface. In laser triangulation, the light spot at the surface of the object is viewed by a linear camera along a direction forming an angle with the illumination axis. The position of the spot on the linear camera is dependent upon the distance of the surface from the device, allowing monitoring the surface location relative to the linear camera. In interferometry with a short coherence length source, a maximum interference signal is observed when the path length along a path to the object is equal to that of a reference path whose length is variable and calibrated. This technique also allows monitoring of the surface location. In the

following embodiments it is shown how the depth evaluation is accomplished by using interferometry with a short coherence length source. Of course, the other methods are also applicable.

[0033] The material for analysis may be opaque or partly transparent. As a result of the high temperature generated by the focused laser beam – ablating beam, a small amount of the material is ablated, vaporized and ionized, its atoms and ions being brought to excited states, thus allowing species in the plasma so formed to be identified by spectrally and temporally resolving the spark light emission in LIPS analysis. The optical emission is analysed with a spectrometer and the spectrum is detected through appropriate optics by, for example, one of a gated photodiode array detector, an intensified CCD camera, and an array of photomultipliers each individually positioned to detect an emission line representative of a given element.

[0034] To perform a reliable depth profile analysis, it is important to ensure a controlled and reproducible ablation rate and a well-characterized ablation volume. The ablation is preferably the same for each laser pulse in terms of radial distribution of the ablated depth. In order to obtain this result, the spatial characteristics of the laser beam are controlled and the laser is preferably stable from pulse to pulse. In particular, to achieve a good depth resolution, all portions of the laser beam throughout its cross-section sample the material at approximately to a same depth. This condition is difficult to satisfy with a near-Gaussian laser beam profile, resulting in cone-shaped craters. Inevitably, for any given Gaussian profiled pulse other than a first, the laser samples material from different depths along the crater surface. Therefore, it is often preferable to tailor the radial distribution of energy in the laser beam for instance by using a diaphragm to select only a homogenous part of the beam so as to produce a crater with flat bottom and steep walls.

[0035] A preferred embodiment is shown in simplified block diagram in Figure 1. A laser source 40 emits a laser beam 10 of sufficient fluence - spatial energy density or energy per unit surface - for ablation. The laser beam 10 is reflected by a mirror 12 through focusing optics 14 and is reflected by a dichroic plate 16. The laser beam 10 propagates through a pierced mirror 18 to a target 20. The focusing optics is optionally disposed at different

locations within the optical path of the laser beam 10 such as between the dichroic plate and the target 20.

[0036] With the aid of a lens 22 and the pierced mirror 18, a reduced image of the plasma is created at the entrance slit of the spectrometer 26 coupled to data processing unit 28. Another mirror 24 is shown for redirecting the light from the plasma and reflected from pierced mirror 18. This configuration allows efficient collection of the light emitted by the plasma 30 formed adjacent the target, the light emitted along the axis of the plasma plume. The optical emission from the plasma is spectrally analyzed. Typically this involves dispersion of the light in dependence upon wavelength thereof using, for example, a grating spectrometer and detecting the dispersed light with a gated detector such as an intensified photodiode array detector, CCD camera, or an array of photomultipliers each individually positioned in the focal plane to detect, simultaneously and during a specified time period, a number of emission lines representative of the different elements in the material to be analyzed. Standard techniques are used to properly synchronize the laser and detector so as to collect the emission signal during a time window providing desired levels of signal-to-noise ratio. Preferably, a fast computer evaluates the sensed spectra and calculates the element concentrations via calibration procedures which are well known to spectroscopists skilled in the art.

[0037] Figure 1 shows the crater depth measuring device, in the form of interferometer 32 with a short coherence length source. In this embodiment, the optical path of light provided by the interferometer 32 leading to and from the sample passes through the dichroic plate 16 and pierced mirror 18.

[0038] The interferometer 32 is optionally configured in a number of forms. Figure 2a shows an embodiment that allows a depth measurement at one point on the sample. The depth evaluation function is realized by a two-wave Michelson interferometer formed with single mode optical fibers. A supra-luminescent diode 40 emitting light with a bandwidth of typically 20 nm is used as light source. Within the optical path of the light emitted from the diode is an optical isolator 42 to prevent optical feedback to the diode from any interface and from the surface of the object, which may affect operation. The beam then propagates

through a splitter/mixer 44, which is a 50-50% bi-directional coupler. The reference path length is varied by collimating the beam with a lens 46 and mounting the mirror 48 on a translation slide. Optionally a retroreflector is used in place of the mirror 48. In the optical path to the sample 50, the beam emerging from the fiber is focused by a lens 52 and directed onto the sample surface. A reflected beam reflected back from the sample and the mirror is combined at the splitter/mixer 44 and interference is measured by a detector 54, deriving data for use in determining the depth of the crater.

[0039] The embodiment shown in Figure 2b enables depth measurements at two points, for example one inside the crater proximate its center and the other one outside the crater in a region unaffected by ablation and residual debris. A second 50-50% bidirectional coupler 60 is used in the optical path to the sample to give two secondary light paths that are separated by a given distance - one path within the bi-directional coupler is unused. A telecentric optical system 62 comprising two lenses is then used to focus light emitted by the source on the sample at two different measurement locations. The two secondary light paths formed by the second 50-50% coupler are not in the same plane so that the two interferometric signals are conveniently separated before the start of any ablation.

[0041] A preferred embodiment of a method of determining the ablation crater profile is depicted in Figure 3a, relies on an interferometer that performs a one-point measurement (as in Figure 2a) and a rotating slide or galvanometer 70 to reflect the interferometer beam emitted by a source 101, so as to scan a line across the crater. The interferometer beam and ablating laser beam emitted by laser 100 are superimposed using a dichroic plate 72 and are substantially colinear. Assuming that the reference path scan in the interferometer is much faster than the scan across the crater, depth information is obtained for each position along a line across the crater from the signal observed at zero path length difference on the interferometer detector. Such a scan is then repeated in order to record the evolution of crater profile as a function of time, either intermittently or simultaneously with a succession of laser ablation events. Alternatively, instead of using a rotating slide or galvanometer, a linear measurement scan on the sample surface is realized by translating the interferometer source along a line transverse to the beam.

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[0042] In order to measure the depth of the crater at several points within a plane covering the whole crater area instead of scanning just a line thereacross, perform several line scans are performed side-by-side with relative motion between the sample and the beam of the optical depth evaluator in a direction perpendicular to line scans.

[0043] In Fig. 3b, a crater depth evaluation is performed using an interferometer that allows a two-point measurement (as the one depicted in Figure 2b). Here two parallel measurement beams 80 and 82 exiting the interferometer 101 are used to perform two depth measurements, one inside the crater proximate its center and the other one outside the crater in a region unaffected by ablation and residual debris. The crater depth is then defined as the distance between the two measurement points in the longitudinal direction. In this case, no scanning across the crater is performed. Typically, by aligning the measuring beam and the ablation beam to have concentric optical axes, the measuring beam results in a measurement of a centre of the crater.

[0044] When only the position of the crater bottom is sought, it is also possible to perform a one-point non-scanning measurement, as depicted in Figure 3c. As the ablating laser repeatedly digs into the sample, the evolution of crater depth is determined using a measurement beam 90 from the interferometer 101. The ablating laser 100 and measurement beam are preferably co-axial. This approach is results in more accurate results when large depth variations occur with each ablating laser pulse.

[0045] Referring to Figure 3d, where the interferometer measurement beam 92 is other than coaxial and has an optical axis thereof at an angle with that of the ablating laser beam, thus eliminating the need for a dichroic plate to superimpose the two beams. It is preferable that the angle relative to a normal from the surface is not so large as to result in shading of the interferometer beam by the crater rim, which would prevent a depth measurement at the crater bottom. This is particularly significant with craters of large aspect ratio. Variations on the configuration of Figure 3d are possible, including a scanning one-point measurement (similar to Figure 3a), or a fixed two-point measurement (similar to Figure 3b). When determining the evolution of crater depth, data processing is needed to account for the angle of the measurement beam relative to normal.

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[0046] For the embodiments described above where a dichroic plate is used to combine the interferometer beam and laser beam, an alternative to providing a dichroic plate that reflects the laser beam and transmits the interferometer beam is a dichroic plate that reflects the interferometer beam and transmits the laser beam. In this case, the scanning approach of Figure 3a is realisable more simply by rotating the dichroic plate itself.

[0047] In tests conducted to validate the above embodiments, the composition of multi-component pharmaceutical tablets having a film coating was analysed by LIPS as a function of the depth, as measured in-situ and in real time by interferometry with a short coherence length source. The core of the tablets contained 10% (by weight) of an active agent bearing a chlorine atom which could be used as a tracer element for the LIPS analysis. The film coating (less than 100 μm thick) contained titanium oxide. The ablation laser was a Nd:YAG solid state laser (emitting at 1064 nm) with a pulse duration of 6 ns (full width at half maximum). The ablation laser energy was 90 mJ per pulse and the repetition rate was 1 s^{-1} . The laser beam was focused to a spot size of approx. 600 μm on the tablet surface. The light emission from the laser-produced plasma was analysed by a 0.66 m spectrograph of the Czerny-Turner type provided with a 1200 grooves/mm holographic grating. The dispersed light was detected by an intensified photo-diode array at the exit port of the spectrograph. The grating was positioned so that a 20-nm wide spectrum centered on 840 nm was recorded. The gated detector was synchronized with the laser pulse so as to integrate light during the period from 1 to 3 μs after the pulse. The in-situ depth evaluation was realized using an interferometer of the type shown in Figure 2a, provided with a supra-luminescent diode operating at 1310 nm. A scanning one-point measurement was performed (as depicted in Figure 3a) so as to obtain line scans across the craters. A line scan included 100 depth measurements on a distance of 3 mm and lasted 1 second, so that a line scan was performed for each laser pulse, thus providing real-time monitoring of the depth of the crater at which analysis is performed.

[0048] Two hundred laser pulses were directed at the same position on a tablet in order to obtain a depth profile. Figure 4 shows two different emission spectra, one obtained at the 3rd pulse at a depth still substantially within the tablet coating, and the other obtained at the 50th pulse, which is well within the tablet core. In the first case, the presence of titanium oxide in

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the coating contributes many prominent titanium lines. Emission from carbon and oxygen is also observed since organic compounds are present in the coating. However, the chlorine line at 837.60 nm is barely noticeable (on the wing of the Ti 837.79 nm line) because the tablet core has not yet been penetrated significantly. After 50 pulses, the reverse is observed. Titanium lines have virtually disappeared, while the chlorine line is readily observed. A weak titanium signal (here seen at 843.5 nm) can persist even when the center of the beam has long penetrated the core of the tablet because the periphery of the laser beam can interact with the walls of the crater (including part of the coating at the surface).

[0049] Figure 5 shows the full evolution of spectral line intensities for the whole 200-pulse series. It was difficult to exploit directly the chlorine line because of interference by the titanium line at 837.79 nm. The dashed line rather shows the emission intensity at 838.25 nm, which is the sum of the titanium signal at this wavelength and of a background signal (see Figure 4). One sees readily that the titanium signal drops rapidly within the first 6 pulses on the surface, indicating complete penetration through the coating. Beyond the 6th pulse, there is a slower decay up to the 20th pulse, after which the intensity is constant at approximately 100 counts, this signal being attributable almost entirely to the background emission. In order to further characterize the transition between the coating and the core, Figure 5 shows the ratio of raw chlorine intensity to raw titanium intensity, i.e. the ratio of the total intensity (line plus background) at 837.6 nm to the total intensity at 838.25 nm. The raw intensities are used so that, even when there is no titanium line, the denominator is not zero because of background emission. One sees that the Cl/Ti ratio steadily increases starting from the 4th or 5th pulse up to approximately the 20th pulse where a plateau is reached. The large spikes observed are attributable to variations of chlorine content in the ablated matter, clearly illustrating the heterogeneous nature of the tablet core, where only 10% of the compacted powder contains chlorine. After about 80 pulses, the Cl/Ti ratio decreases because of changes in laser-target interaction and of plasma confinement attributable to the larger aspect ratio of the crater. The Cl/Ti ratio then settles at a value between 1 and 2. In the absence of chlorine and titanium lines, the intensity ratio corresponds to a ratio of background signals at very close wavelengths, which would be equal to 1. In fact, the chlorine is still detected after 200 pulses, thus giving a ratio larger than 1.

A7 [0050] Figure 6 shows the evolution of the crater profile obtained with 220 successive line scans of the depth measurement beam. The 200 ablation laser pulses occurred from the 10th to the 210th line scan. The crater depth is seen to steadily increase with the number of laser pulses. Near the end, the crater is found to have rather steep walls and the crater width is approximately 600 μm , corresponding to the laser spot size.

[0051] Figure 7 shows part of the data of Figure 6, i.e. the evolution with scan number of the depth at the bottom of the crater. The depth starts to increase at the 10th scan when the first laser pulse is fired. The final depth (at the 210th scan) is approximately 1.9 mm, corresponding to a crater aspect ratio of approximately 3 (i.e. 1.9/0.6). Some discontinuities are observed in the profile, for instance between the 80th and 90th scan, indicating that large powder particles are sometimes removed suddenly from the target. Another feature of the depth profile shown in Figure 7 is the change in ablation regime at approximately the 160th scan (i.e. 150th laser pulse), where the ablation rate (depth ablated per laser pulse) is seen to decrease. This shows that a depth calibration based on the number of pulses is not applicable to the whole sequence of pulses for this case, thus illustrating the usefulness of the present invention in providing an in-situ and real-time measurement of the actual depth reached by each ablating laser pulse.

[0052] Figure 8 shows the full realization of the present invention, the depth information (from Figure 7) being combined with the compositional analysis (from Figure 5). This figure directly provides the location of various heterogeneities in the tablet. In particular, one may determine the coating thickness from the depth profile of the Ti line, namely by defining the thickness as the halfway point of the steep decay of titanium signal. This point is reached between the 4th and 5th laser pulses. Since the depths reached after these pulses were 46 and 56 μm respectively, the coating is likely approximately 50 μm thick.

Please add Claims 26-57:

A8 26. A method of compositional analysis of a heterogeneous material of one or more components, comprising the steps of:

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- (a) directing a pulse of laser radiation at a target of the heterogeneous material to ablate an amount thereof, and to form an ablation crater having a depth;
 - (b) determining the concentration of one or more selected components in the heterogeneous material ablated from the target;
 - (c) measuring in situ the depth of the ablation crater other than in dependence upon time gated imaging data of the directed pulse of laser radiation, and
 - (d) determining a composition of the heterogeneous material at the depth.

27. A method according to claim 26, wherein the step of measuring the depth is performed based on sensing of a beam of light directed at the target and other than the pulse of laser radiation.

28. A method according to claim 26, wherein at least one of steps (a) to (d) is repeated for determining a compositional profile of the heterogeneous material as a function of the depth.

29. A method according to claim 28, further comprising the steps of:

- (e) shifting a target to a each of a plurality of locations across the heterogeneous material, and
- (f) repeating steps (a) to (e).

30. A method according to claim 29 comprising the steps of determining a compositional profile of the heterogeneous material in three dimensions.

31. A method according to claim 28, wherein the step of measuring the depth of the ablation crater further comprises a steps of:

- (g) measuring the depth of the ablation crater at each of a plurality of points thereacross; and
- (h) generating a depth profile of the ablation crater.

32. A method according to claim 31, further comprising the steps of:

- (h) repeating step (h) at a plurality of depths of the ablation crater; and
- (i) generating an evolution of the depth profile of the ablation crater.

33. A method according to claim 29, wherein the step of measuring the depth of the ablation crater further comprises a step of:
- (j) measuring the depth of the ablation crater at each of a plurality of points thereacross for each of a plurality of ablation craters; and
 - (k) generating a compositional profile of the heterogeneous material in three dimensions.
34. A method according to claim 28, further comprising a step of processing data from steps (a) to (d) to align one with another spatially for forming the compositional profile of the heterogeneous material as a function of the depth.
35. A method according to claim 29, further comprising a step of processing data from steps (a) to (d) to align one with another spatially for forming the compositional profile of the heterogeneous material as a function of the depth.
36. A method according to claim 26, wherein the concentration is determined by a spectrochemical analysis technique selected from a group consisting of: optical emission spectrometry of the light emitted by the plasma produced above the target concomitantly with the laser ablative event; optical emission spectrometry, following the introduction of the material ablated from the target into an auxiliary plasma discharge where said material is excited to emit light; and mass spectrometry of said material ablated from the target, following the introduction of the ablated material into said auxiliary plasma discharge, from which the ablated material is extracted in ionized form.
37. A method according to claim 26, wherein the step of measuring the depth is performed by a technique selected from a group consisting of: confocal microscopy, laser triangulation, and interferometry using a short coherence length light source.
38. A method according to claim 37, wherein the step of measuring the depth comprises the steps of:
- directing a beam of short coherence length light toward both the ablation crater and an interferometric mirror; and

measuring interference between light reflected from the ablation crater and reflected from the interferometric mirror.

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39. A method according to claim 38, comprising steps of:
directing a beam of short coherence length light toward both another location within the ablation crater and the interferometric mirror;
measuring interference between light reflected from the other location within the ablation crater and reflected from the interferometric mirror; and
generating a depth profile of the ablation crater.
40. A method according to claim 37, further comprising the steps of:
directing a beam of short coherence length light toward a surface inside the ablation crater, a surface outside the ablation crater and an interferometric mirror, and
measuring interference between light reflected from the surface inside the ablation crater and the interferometric mirror and between light reflected from the surface outside the ablation crater and the interferometric mirror.
41. A method according to claim 38 wherein the short coherence light propagates colinearly with the laser radiation.
42. A method according to claim 38 wherein the short coherence light propagates at an angle to the direction of the laser radiation.
43. An apparatus for compositional analysis of a heterogeneous material of one or more components, comprising:
a laser source for producing an ablation beam of laser pulses of sufficient fluence to ablate an amount of the heterogeneous material from a target under study and thereby to form an ablation crater of a depth;
a spectrometric device for detecting and determining the concentration of one or more selected components in the heterogeneous material ablated from the target;
and,

an optical device for measuring in situ the depth of the ablation crater using other than time gated imaging.

44. An apparatus according to claim 43, wherein said optical device comprises a light source for directing light at the heterogeneous material and a sensor for sensing the light from the light source.

45. An apparatus according to claim 43, wherein said spectrometric device is selected from a group consisting of: an optical spectrometric device for a spectrochemic analysis using light emitted by plasma produced above the target concomitantly with the laser ablative event; an optical spectrometric device for a spectrochemic analysis using light emitted by an auxiliary plasma discharge into which the material ablated from the target is introduced; and a mass spectrometer for determining the concentration of one or more selected components in the material ablated from the target and subsequently ionized.

46. An apparatus according to claim 43, wherein the optical device for measuring the depth of the ablation crater is selected from a group consisting of a confocal microscopy device, a laser triangulation device, and an interferometer relying on a short coherence length light source.

47. An apparatus according to claim 43, comprising a mechanical device for scanning a beam of the optical device across the target for measuring the depth of the ablation crater.

48. An apparatus according to claim 43, comprising an actuator for effecting relative motion between the beam of the optical device and the target.

49. An apparatus according to claim 43, wherein the optical device for measuring the depth of the ablation crater comprises a dual measuring beam system for simultaneous measurement of depth at two points on the sample surface.

50. An apparatus according to claim 43, wherein the optical device for measuring the depth of the ablation crater comprises a dual measuring beam system for simultaneous measurement of depth at two points on the sample surface simultaneously, one proximate a

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point where the laser source directs a beam at an instance of time and another in a region substantially unaffected by the ablation beam and residual debris at the instant of time.

51. An apparatus according to claim 43, comprising a dichroic plate disposed for receiving the ablation beam and a beam from the optical device for superimposing them so as to be substantially collinear in use.

52. An apparatus according to claim 43, wherein said optical device is disposed relative to the laser source for providing a beam forming an angle relative to the ablation beam.

53. An apparatus according to claim 43, comprising means for generating the ablation beam of substantially uniform radial distribution of energy, thus producing a crater with flat bottom and steep walls.

54. An apparatus according to claim 43, comprising an aperture disposed for having the ablation beam pass therethrough for resulting in an ablation beam of substantially uniform radial distribution of energy.

55. An apparatus according to claim 43, comprising a data processor for processing data from the spectrometric device and the optical device to correlate data provided by each.

56. An apparatus according to claim 43, comprising a data processor for processing data from the spectrometric device and the optical device to correlate data provided by each for spatially orienting a plurality of data one relative to another.

57. An apparatus for compositional analysis of a heterogeneous material of one or more components, comprising:

a laser source for producing an ablation beam of laser pulses of sufficient fluence to ablate an amount of the heterogeneous material from a target under study and thereby to form an ablation crater of a depth;

a spectrometric device for detecting and determining the concentration of one or more selected components in the heterogeneous material ablated from the target;

a light source for directing light at the heterogeneous material;

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a sensor for in situ sensing of the light from the light source and for providing sensor data; and

a processor for determining the depth of the ablation crater in dependence upon the sensed data.

ATTACHMENT C
Marked up version showing the changes made

A marked up version showing the changes made to the replacement paragraphs is provided as follows:

0006, 0010, 0011, 0012, 0014, 0015, 0016, 0026, 0027, 0028, 0031, 0032, 0033, 0034, 0035, 0036, 0037, 0038, 0039, 0041, 0042, 0043, 0044, 0045, 0046, 0047, 0048, 0049, 0050, 0051 and 0052.

Please delete paragraph 0017.

[0006] Laser radiation, on the other hand, possesses several attributes that make it particularly well suited for the task of analyzing heterogeneous materials. In so-called laser ablation, a focused laser pulse provides locally a very large power density that transforms a small amount of solid material directly into a vapor plume suitable for further analysis. The possibility of concentrating laser radiation on a very small surface enables the sampling and analysis of heterogeneous materials with very good lateral resolution (down to a few micrometers). The separate analysis of successive laser ablation events at a same position on the solid material also enables a depth-resolved analysis, the depth reached by each laser [shot] pulse ranging from tens of nanometers to tens of micrometers depending on the laser characteristics and material type.

[0010] In order to establish a detailed depth profile, one needs to perform several compositional measurements at different depths in the material. To avoid repeatedly carrying the sample to a separate instrument for the determination of depth, and the subsequent need for precise repositioning of the sample in the laser ablation apparatus, one can resort to a preestablished calibration of the crater depth on the basis of the cumulative number of laser [shots] pulses. In this way, the compositional analysis for a given laser [shot] pulse is made to correspond to a given depth. In cases where the sample comprises a coating and a substrate, both having significantly different ablation rates (ablated depth per laser [shot] pulse), different calibrations can be used for the coating and substrate, and an interpolation can be used for the interface region. This procedure assumes that the ablation rate is the same for the study sample and the calibration sample, which in particular requires

sufficient stability of the laser pulse energy and beam radial profile. However, this approach is limited to relatively simple cases. It would not be applicable to samples for which the ablation rate varies in a continuous manner as a function of depth, or to complex multilayer samples.

[0011] An example of such a problematic case is the compositional mapping of pharmaceutical tablets by LIPS. The core of pharmaceutical tablets consists of a compacted blend of different components (active agent, lubricant, inactive excipient, etc.) originally in powder form, and may be coated with a film (typically containing titanium dioxide and other ingredients). US Patent 5,781,289 July 14, 1998 by Sabsabi and Bussière describes the use of LIPS for the analysis of preselected components in homogeneous pharmaceutical compositions, for example for the quantification of the average active agent concentration in tablets. Although such a spatially-averaged analysis by LIPS can find several uses in pharmaceutical process development and control, a mapping capability would prove useful for another set of problems: (i) assessment of powder blend uniformity by the mapping in tablets of the drug, lubricant or other components, or (ii) evaluation of coating homogeneity and thickness across the surface of the tablet. In the latter case, a depth-profiling capability is required. However, because of the particular laser-matter interaction that occurs in tablets and of the granular nature of tablets, the corresponding ablation rate is usually very large compared to that in a metal for instance. Whereas on a metal tens of nanometers are ablated per laser [shot] pulse, 10-15 μm can be ablated per pulse in a tablet coating and up to 50-100 μm per [shot] pulse in the core of tablets. As a result, the aspect ratio (depth-to-diameter ratio) of the laser-produced crater can grow very large, thus significantly modifying the ablation rate at each successive [shot] pulse (because of a decreasing laser energy density on the crater surface due to an increasing exposed surface, or because of increasing confinement of the ablated matter and of plasma in the crater). A depth calibration in this case would not be possible. The same would be true if instead of using LIPS, the analysis proceeded through the transfer of the ablated matter to an auxiliary discharge and detection system (as in LA-ICP-OES or LA-ICP-MS). The same would also be true of any other analysis based on direct solid sampling by laser ablation where the ablation rate varies continuously as a function of depth, or where the multilayer structure of the sample is so complex as to preclude any calibration.

[0012] Combining laser ablative sampling and optical sensing of the sampling position in a single integrated apparatus would provide a means of determining in real time the depth of laser-produced craters for each laser [shot] pulse if desired, thus eliminating the need for depth calibration. US Patent 6,259,530 B1 July 10, 2001 by Monsallut describes a method and device, based on optical heterodyne interferometry, for measuring the depth of craters obtained by the bombardment, with a beam of primary ions, of a sample placed in the analysis chamber of a physico-chemical analyzer, such as a SIMS instrument. This invention relates to depth-profile analysis by ion-based techniques in high-vacuum chambers. It does not feature an integrated optical system performing both functions of laser-ablative sampling and crater-depth evaluation. Moreover, this method requires the optical paths to follow an incident direction inclined in relation to the surface of the sample (thus freeing the space needed for the circulation of secondary ions extracted from the sample). Consequently, this configuration would not be adequate for the characterization of craters with large aspect ratio, since shading might occur.

[0014] Therefore, there is a need to provide an optical tool for the non-contact, in-situ and real-time measurement of the depth of laser-produced craters, for each laser [shot] pulse or at any [shot] pulse number interval desired. The in situ and real time measurement of depth eliminates the need to periodically characterize the crater depth in another separately-located instrument, or to rely on a calibration of depth (based on cumulative [shot] pulse number) for a given material, or finally to resort to an interpolation of such calibrations for describing the interface between two materials.

[0015] [In one aspect, the invention is to provide a rapid and accurate three-dimensional compositional mapping of heterogeneous materials, which in particular may feature large changes in composition and physical properties as a function of depth. Accordingly, this invention consists in a new method and apparatus for simultaneously measuring the composition of ablated matter and the crater depth corresponding to a given laser ablation event, thus providing a more rapid and accurate compositional depth profile than achievable by current methods and instrumentation.] In accordance with the invention there is provided a method of compositional analysis of a heterogeneous material of one or more components, comprising the steps of: directing a pulse of laser

radiation at a target of the heterogeneous material to ablate an amount thereof, and to form an ablation crater having a depth; determining the concentration of one or more selected components in the heterogeneous material ablated from the target; (c) measuring in situ the depth of the ablation crater other than in dependence upon time gated imaging data of the directed pulse of laser radiation, and (d) determining a composition of the heterogeneous material at the depth.

[0016] [In accordance with another aspect, the invention is directed to a method of compositional analysis of a heterogeneous material of one or more components. The method comprises steps of: (a) directing a pulse of laser radiation at a target of the heterogeneous material to ablate an amount thereof, and to form an ablation crater having a depth and (b) determining the concentration of one or more selected components in the heterogeneous material ablated from the target. The method further includes steps of (c) measuring the depth of the ablation crater, and (d) determining in situ and in real time a composition of the heterogeneous material at the depth.] In accordance with another aspect of the invention there is provided an apparatus for compositional analysis of a heterogeneous material of one or more components, comprising: a laser source for producing an ablation beam of laser pulses of sufficient fluence to ablate an amount of the heterogeneous material from a target under study and thereby to form an ablation crater of a depth; a spectrometric device for detecting and determining the concentration of one or more selected components in the heterogeneous material ablated from the target; and an optical device for measuring in situ the depth of the ablation crater using other than time gated imaging.

[0026] Figure 5 shows the evolution of spectral line intensities obtained by LIPS as a function of the number of laser [shots] pulses.

[0027] Figure 6 shows the evolution of the crater profile obtained with 220 successive line scans of the depth measurement beam. The 200 ablation laser [shots] pulses occurred from the 10th to the 210th line scan.

[0028] Figure 7 shows the evolution of crater depth as a function of the scan number. The 200 ablation laser [shots] pulses occurred from the 10th to the 210th line scan of the depth measurement beam.

[0031] In addition to these two functions, a complete analytical apparatus must also include the means for analysing the composition of the ablated matter. In the LIPS technique, the luminous plasma formed above the specimen surface concomitantly with the ablation event is analysed through optical emission spectrometry. Different elements present in the sample are identified by the emission of characteristic spectral lines at well-known wavelengths. Furthermore, their concentration [can be deduced] is deduceable from the spectral line intensity, following calibration using certified standard materials. In general, time gating of the detection device is used so as to eliminate the very intense and less useful continuous and ionic emission of the first instants of the laser-produced plasma. In other techniques, the sample is enclosed in an ablation chamber comprising a window through which the ablating laser [can be] is focused. After extinction of the laser-produced plasma, the ablated and atomized matter recondenses in aerosol form and is transported in a gas [stream (usually argon)] stream, for example argon, toward an auxiliary continuous plasma device, [usually] for example an inductively-coupled plasma (ICP). The ablated material [can also be] is optionally introduced directly into the auxiliary plasma device, for example a microwave-induced plasma device [(Uebbing et al.), which connects directly with the laser ablation chamber, as described by Uebbing et al. in Spectrochim. Acta Part B, vol. 47, 1992, p. 611], which connects directly with the laser ablation chamber]. The aerosol is again atomized and ionized in the auxiliary plasma device, with some of the atoms and ions being brought to excited states. The detection of excited atoms or ions by optical emission spectroscopy [(as in LIPS) can] as in LIPS, for example, is then be used to identify and quantify the elements present. Alternatively, the quantitative elemental analysis [can be] is performed following the extraction and mass-separation of ions by electrostatic [means] methods, for example using a mass spectrometer. Although in the present [invention] embodiment the ablated matter i[may be] s introduced in such a way into an auxiliary plasma to perform the spectrochemical analysis, the preferred embodiments described below rather integrate the LIPS scheme. It allows more flexibility in terms of sample [shape and size or] shape, size and even movement since the sample does not have to be enclosed in an ablation chamber.

[0032] The depth at which each measurement is made [has to be] is preferably evaluated in-situ and in real time. Depth evaluation [can be] is optionally based on confocal

microscopy, laser triangulation or interferometry using a short coherence length light source [also called] - also referred to as white light interferometry or optical coherence tomography. In confocal microscopy, light is sent through a pinhole and the light collected through the same pinhole after reflection by the object is monitored. The surface location is determined by noting that the collected light is at maximum intensity when the image of the pinhole is [at] in focus on the surface. In laser triangulation, the light spot at the surface of the object is viewed by a linear camera along a direction [making] forming an angle with the illumination axis. The position of the spot on the linear camera is dependent upon the distance of the surface from the device, [which allows] allowing monitoring the surface location relative to the linear camera. In interferometry with a short coherence length source, a maximum interference signal is observed when the path length along [the arm going] a path to the object is equal to that of a reference [arm] path whose length is [varied. This variation being calibrated, this] variable and calibrated. This technique also allows monitoring of the surface location. [The] In the following embodiments [show] it is shown how the depth evaluation [can be] is accomplished by using interferometry with a short coherence length source. Of course, the other methods are also applicable.

[0033] The material [to be analyzed] for analysis may be opaque or partly transparent. As a result of the high temperature generated by the focused laser beam – ablating beam, a small amount of the material is ablated, vaporized and ionized, its atoms and ions being brought to excited states, thus allowing species in the plasma so formed to be identified by spectrally and temporally resolving the spark light emission [in LIPS)] in LIPS analysis. The optical emission is analysed with a spectrometer and the spectrum is detected through appropriate optics by, for example, one of a gated photodiode array detector, an intensified CCD camera, [or by] and an array of photomultipliers each individually positioned to detect an emission line representative of a given element.

[0034] To perform a reliable depth profile analysis, it is important to ensure a controlled and reproducible ablation rate and a well-characterized ablation volume. The ablation [has to be] is preferably the same for each [shot] laser pulse in terms of radial distribution of the ablated depth. In order to obtain this result, the spatial characteristics of the laser beam [have to be] are controlled and the laser [needs to be] is preferably stable from [shot to shot]

pulse to pulse. In particular, to achieve a good depth resolution, all [parts] portions of the laser beam throughout its cross-section sample the material at approximately [the] to a same depth. This condition is difficult to satisfy with a near-Gaussian laser [beam, which produces cone] beam profile, resulting in cone-shaped craters. Inevitably, for any given [shot (except the first), the laser will sample] Gaussian profiled pulse other than a first, the laser samples material from different depths along the crater surface. Therefore, [one may want] it is often preferable to tailor the radial distribution of energy in the laser beam for instance by using a diaphragm to select only a homogenous part of the beam so as to produce a crater with flat bottom and steep walls.

[0035] [One of the preferred embodiments is shown in Figure 1. In the Figure, the] A preferred embodiment is shown in simplified block diagram in Figure 1. A laser source 40 emits a laser beam 10 of sufficient fluence [(spatial) - spatial energy density or energy per unit (surface) for ablation.] surface - for ablation. The laser beam 10 is reflected by a mirror 12 through focusing optics 14 and is reflected by a dichroic plate 16. The laser beam [goes further] 10 propagates through a pierced mirror 18 to a target 20. The focusing optics [may also be placed after] is optionally disposed at different locations within the optical path of the laser beam 10 such as between the dichroic plate and the target 20.

[0036] With the aid of a lens 22 and the pierced mirror 18, a reduced image of the plasma is created at the entrance slit of the spectrometer [26, which is coupled to] 26 coupled to data processing unit 28. Another mirror 24 [may be provided to redirect] is shown for redirecting the light from the plasma and reflected from pierced mirror 18. This configuration allows efficient collection of the light emitted by the plasma 30 formed adjacent the target, the light emitted along the axis of the plasma plume[using a pierced mirror]. The optical emission from the plasma is spectrally [analyzed using] analyzed. Typically this involves dispersion of the light in dependence upon wavelength thereof using, for example, a grating spectrometer and detecting the [equipped] dispersed light with a gated detector such as an intensified photodiode array detector, CCD camera, or an array of photomultipliers each individually positioned in the focal plane to detect, simultaneously and during a specified time period, a number of emission lines representative of the different elements in the material to be analyzed. Standard techniques are used to properly synchronize the laser and

detector so as to collect the emission signal during a time window providing [the best] desired levels of signal-to-noise [ratio, while] ratio. Preferably, a fast computer evaluates the [measured]sensed spectra and calculates the element concentrations via calibration procedures which are well known to spectroscopists skilled in the art.

[0037] Figure 1 [also] shows [how] the crater depth [evaluator, namely an]measuring device, in the form of interferometer 32 with a short coherence length source~~l~~[is an integral part of the apparatus of the present invention]. . In this embodiment, the optical path of light provided by the interferometer 32 leading to and from the sample passes through the dichroic plate 16 and pierced mirror 18.

[0038] The interferometer [depicted in Figure 1 may take several] 32 is optionally configured in a number of forms. Figure 2a shows an embodiment that allows a depth measurement at one point on the sample. The depth evaluation function is realized by a two-wave Michelson interferometer [made of]formed with single mode optical fibers. A supra-luminescent diode 40 emitting light with a bandwidth of typically 20 nm is used as light source. [This diode is followed by] Within the optical path of the light emitted from the diode is an optical isolator 42 to prevent optical feedback to the diode from any interface and from the surface of the [object of affecting its] object, which may affect operation. The beam [is then fed] then propagates through a splitter/mixer 44, which is a 50-50% bi-directional coupler. The reference [arm] path length is varied by collimating the beam with a lens 46 and mounting the mirror 48 [(or a retroreflector)] on a translation slide. Optionally a retroreflector is used in place of the mirror 48. In the [arm going] optical path to the sample 50, the beam emerging from the fiber is focused by a lens 52 and directed onto the sample surface. [Laser] A reflected beam reflected back from the sample and the mirror is combined at the splitter/mixer 44 and interference is measured by a detector 54, deriving data for use in determining the depth of the crater [on the sample].

[0039] The embodiment shown in Figure 2b enables depth measurements at two points, for example one inside the crater [at] proximate its center and the other one outside the crater in a region unaffected by ablation and residual debris. A second 50-50% bidirectional coupler 60 is used in the [arm going] optical path to the sample to give two secondary light

[sources] paths that are separated by a given distance - [(one arm of this) one path within the bi-directional coupler is unused[]]. A telecentric optical system 62 [made of] comprising two lenses is then used to focus [them on the sample] light emitted by the source on the sample at two different measurement locations. The two secondary [sources given] light paths formed by the second 50-50 % coupler are not in the same plane so that the two interferometric signals are conveniently separated before the start of any ablation.

[0041] [In order to determine] A preferred embodiment of a method of determining the ablation crater [profile, or simply the crater depth, several approaches are possible. One preferred embodiment,] profile is depicted in Figure 3a, [consists in using] relies on an interferometer that performs a one-point measurement (as in Figure 2a) and a rotating slide or galvanometer 70 to reflect the interferometer beam emitted by a source 101, so as to scan a line across the crater. The interferometer beam and ablating laser beam emitted by laser 100 are superimposed using a dichroic plate 72 and are substantially colinear. Assuming that the reference [arm] path scan in the interferometer is much faster than the scan across the crater, depth information is obtained for each position along a line across the crater from the signal observed at zero path length difference on the interferometer detector. Such a scan [can be] is then repeated in order to record the evolution of crater profile as a function of time, either intermittently or simultaneously with a succession of laser ablation events. [Instead] Alternatively, instead of using a rotating slide or galvanometer, a linear measurement scan on the sample surface [may be] is realized by translating the interferometer source along a line transverse to the beam.

[0042] In order to measure the depth of the crater at several points within a plane covering the whole crater area instead of scanning just a [line, one may] line thereacross, perform several [such] line scans are performed side-by-side [by moving] with relative motion between the sample [or] and the beam of the optical depth evaluator in a direction perpendicular to [a line scan] line scans.

[0043] [A] In Fig. 3b, a crater depth evaluation [may also be] is performed using an interferometer that allows a two-point measurement (as the one depicted in Figure 2b). [Such an approach is illustrated in Figure 3b, where] Here two parallel measurement beams

80 and 82 exiting the interferometer 101 are used to perform two depth measurements, one inside the crater [at] proximate its center and the other one outside the crater in a region unaffected by ablation and residual debris. The crater depth is then defined as the distance between the two measurement points in the longitudinal direction. In this case, no scanning across the crater is [necessary]. performed. Typically, by aligning the measuring beam and the ablation beam to have concentric optical axes, the measuring beam results in a measurement of a centre of the crater.

[0044] When only the position of the crater bottom is sought, it is also possible to perform a one-point non-scanning measurement, as depicted in Figure 3c. As the ablating laser repeatedly digs into the sample, the evolution of crater depth [can be] is determined using a measurement beam 90 from the interferometer 101. The ablating laser 100 and measurement beam are [collinear] preferably co-axial. This approach [will give better results (in terms of accuracy)] is results in more accurate results when large depth variations occur with each ablating laser [shot] pulse.

[0045] [Yet another possible approach is the one depicted in] Referring to Figure 3d, where the interferometer measurement beam 92 is [not collinear but] other than coaxial and has an optical axis thereof at an angle with that of the ablating laser beam, thus eliminating the need for a dichroic plate to superimpose the two beams. [With this approach, one needs to be careful] It is preferable that the angle relative to a normal from the surface is not so large as to [allow] result in shading of the interferometer beam by the crater rim, which would prevent a depth measurement at the crater [bottom (especially)] bottom. This is particularly significant with craters of large aspect ratio [)]. Variations on the configuration of Figure 3d are possible, including a scanning one-point measurement (similar to Figure 3a), or a fixed two-point measurement (similar to Figure 3b). [In all cases, when] When determining the evolution of crater depth, data processing is needed to account for the angle of the measurement beam relative to normal.

[0046] For [all] the embodiments described above where a dichroic plate is used to combine the interferometer [and laser beams, another variation is possible where instead of] beam and laser beam, an alternative to providing a dichroic plate that reflects the laser beam

and transmits the interferometer [beam, one provides] beam is a dichroic plate that reflects the interferometer beam and transmits the laser beam. In this case, the scanning approach of Figure 3a [could be realized] is realizable more simply by rotating the dichroic plate itself.

[0047] In tests conducted to validate [this invention] the above embodiments, the composition of multi-component pharmaceutical tablets having a film coating was analysed by LIPS as a function of the depth, as measured in-situ and in real time by interferometry with a short coherence length source. The core of the tablets contained 10% (by weight) of an active agent bearing a chlorine atom which could be used as a tracer element for the LIPS analysis. The film coating (less than 100 μm thick) contained titanium oxide. The ablation laser was a Nd:YAG solid state laser (emitting at 1064 nm) with a pulse duration of 6 ns (full width at half maximum). The ablation laser energy was 90 mJ per pulse and the repetition rate was 1 s^{-1} . The laser beam was focused to a spot size of approx. 600 μm on the tablet surface. The light emission from the laser-produced plasma was analysed by a 0.66 m spectrograph of the Czerny-Turner type provided with a 1200 grooves/mm holographic grating. The dispersed light was detected by an intensified photo-diode array at the exit port of the spectrograph. The grating was positioned so that a 20-nm wide spectrum centered on 840 nm [could be] was recorded. The gated detector was synchronized with the laser pulse so as to integrate light during the period from 1 to 3 μs after the pulse. The in-situ depth evaluation was realized using an interferometer of the type shown in Figure 2a, provided with a supra-luminescent diode operating at 1310 nm. A scanning one-point measurement was performed (as depicted in Figure 3a) so as to obtain line scans across the craters. A line scan included 100 depth measurements on a distance of 3 mm and lasted 1 second, so that a line scan was performed for each laser sho[shot] pulse, thus providing real-time monitoring of the depth of the crater at which analysis is performed.

[0048] Two hundred laser [shots were fired] pulses were directed at the same position on a tablet in order to obtain a depth profile. Figure 4 shows two different emission spectra, one obtained at the 3rd [shot] pulse at a depth still substantially within the tablet coating, and the other obtained at the 50th [shot] pulse, which is well within the tablet core. In the first case, the presence of titanium oxide in the coating contributes many prominent titanium lines. Emission from carbon and oxygen is also observed since organic compounds are

present in the coating. However, the chlorine line at 837.60 nm is barely noticeable (on the wing of the Ti 837.79 nm line) because the tablet core has not yet been penetrated significantly. After 50 [shots] pulses, the reverse is observed. Titanium lines have virtually disappeared, while the chlorine line is readily observed. A weak titanium signal (here seen at 843.5 nm) can persist even when the center of the beam has long penetrated the core of the tablet because the periphery of the laser beam can interact with the walls of the crater (including part of the coating at the surface).

[0049] Figure 5 shows the full evolution of spectral line intensities for the whole 200-[shot]pulse series. It was difficult to exploit directly the chlorine line because of interference by the titanium line at 837.79 nm. The dashed line rather shows the emission intensity at 838.25 nm, which is the sum of the titanium signal at this wavelength and of a background signal (see Figure 4). One sees readily that the titanium signal drops rapidly within the first 6 [shots]pulses on the surface, indicating complete penetration through the coating. Beyond the 6th [shot]pulse, there is a slower decay up to the 20th [shot]pulse, after which the intensity is constant at approximately 100 counts, this signal being attributable almost entirely to the background emission. In order to further characterize the transition between the coating and the core, Figure 5 shows the ratio of raw chlorine intensity to raw titanium intensity, i.e. the ratio of the total intensity (line plus background) at 837.6 nm to the total intensity at 838.25 nm. The raw intensities are used so that, even when there is no titanium line, the denominator is not zero because of background emission. One sees that the Cl/Ti ratio steadily increases starting from the 4th or 5th [shot]pulse up to approximately the 20th [shot]pulse where a plateau is reached. The large spikes observed are attributable to variations of chlorine content in the ablated matter, clearly illustrating the heterogeneous nature of the tablet core, where only 10% of the compacted powder contains chlorine. After about 80 [shots]pulses, the Cl/Ti ratio decreases because of changes in laser-target interaction and of plasma confinement attributable to the larger aspect ratio of the crater. The Cl/Ti ratio then settles at a value between 1 and 2. In the absence of chlorine and titanium lines, the intensity ratio [would correspond] corresponds to a ratio of background signals at very close wavelengths, which would be equal to 1. In fact, the chlorine is still detected after 200 [shots] pulses, thus giving a ratio larger than 1.

[0050] Figure 6 shows the evolution of the crater profile obtained with 220 successive line scans of the depth measurement beam. The 200 ablation laser [shots] pulses occurred from the 10th to the 210th line scan. The crater depth is seen to steadily increase with the number of laser [shots] pulses. Near the end, the crater is found to have rather steep walls and the crater width is approximately 600 μm , corresponding to the laser spot size.

[0051] Figure 7 shows part of the data of Figure 6, i.e. the evolution with scan number of the depth at the bottom of the crater. The depth starts to increase at the 10th scan when the first laser [shot] pulse is fired. The final depth (at the 210th scan) is approximately 1.9 mm, corresponding to a crater aspect ratio of approximately 3 (i.e. 1.9/0.6). Some discontinuities are observed in the profile, for instance between the 80th and 90th scan, indicating that large powder particles are sometimes removed suddenly from the target. Another feature of the depth profile shown in Figure 7 is the change in ablation regime at approximately the 160th scan (i.e. 150th laser [shot] pulse), where the ablation rate (depth ablated per laser [shot] pulse) is seen to decrease. This shows that a depth calibration based on the number of [shots would not be] pulses is not applicable to the whole sequence of [shots in] pulses for this case, thus illustrating the usefulness of the present invention in providing an in-situ and real-time measurement of the actual depth reached by each ablating laser [shot] pulse.

[0052] Figure 8 shows the full realization of the present invention, the depth information (from Figure 7) being combined with the compositional analysis (from Figure 5). This figure directly provides the location of various heterogeneities in the tablet. In particular, one may determine the coating thickness from the depth profile of the Ti line, namely by defining the thickness as the halfway point of the steep decay of titanium signal. This point is reached between the 4th and 5th laser shots [shots] pulses. Since the depths reached after these pulses were 46 and 56 μm respectively, [we may then conclude that] the coating is likely approximately 50 μm thick.